Chemokines in the Biology of Lung Cancer

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This is a brief review of some of the mechanisms by which members of the large family of chemotactic cytokines (known as chemokines) participate in critical features of lung cancer biology.

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Chemokines are a family of small (8–12 kDa) cytokines consisting of four subfamilies defined by the configuration of the first two of four conserved cysteine residues (C, CC, CXC, and CXXXC families).[1] Chemokines were initially studied for their ability to recruit specific subpopulations of leukocytes. However, research shows that many if not most of the members of the CC and CXC chemokine families are involved in mediating critical features of tumor biology, such as cell growth, angiogenesis, and metastasis, in addition to regulating tumor immunity. In this review, we briefly outline some of the mechanisms by which chemokines participate in two aspects of tumor biology, angiogenesis and metastasis.

The CXC chemokines can be divided into members that promote angiogenesis (all of which have in common the glutamic acid-leucine-arginine sequence, the "ELR motif," immediately preceding the first cysteine in the NH_3-terminus; the ELR-CXC chemokines), and those that can directly inhibit angiogenesis (which, interestingly, are the interferon-inducible CXC chemokines CXCL9, CXCL10, and CXCL11). These angiostatic CXC chemokines may mediate many of the antiangiogenic and antitumor immune effects of interferons, a phenomenon referred to as "immunoangiostasis" by Strieter et al.[2] This dichotomy in the CXC chemokine family makes them unique among cytokines that regulate angiogenesis. We and others have shown that the ELR-CXC chemokines are major sources of angiogenic activity in non-small cell lung cancer, and that their expression in tumor homogenates correlates strongly with the vascularity of the corresponding tissue section.[3–6]

Many studies have shown that a transcription factor, nuclear factor kappa-B (NFκB), is constitutively activated in cancer cells.[7] This NFκB activity in lung cancer cells is critical to the constitutive production of angiogenic CXC chemokines by malignant cells.[8] Importantly, nonmalignant cells also play a role in promoting angiogenesis. Macrophages and fibroblasts within the tumor are also activated (both by cell-matrix adhesive interactions and by soluble factors present within the tumor) to produce significant quantities of angiogenic CXC chemokines.[9–11] A critical report by Addison and colleagues showed that the endothelial receptor through which CXC chemokines induce angiogenesis is

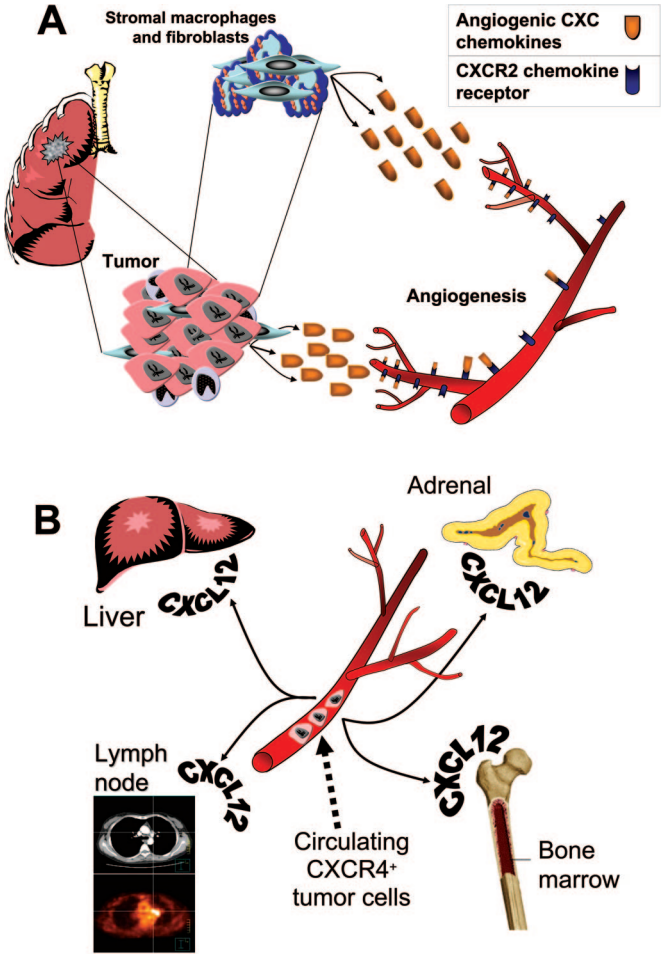

FIGURE 1. (*A*) Angiogenic CXC chemokines (bullet shaped) derived from both malignant cells and tumor-infiltrating stromal cells induce angiogenesis by binding to CXCR2 present on tumor endothelium. (*B*) Stromal cell-derived factor 1 (now known as CXCL12) is constitutively produced in lymph nodes, liver, bone marrow, and the adrenal gland. This results in preferential "recruitment" to these organs of circulating tumor cells that express CXCR4.

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CXCR2.[12,13] In summary, ELR-CXC chemokines are an important source of angiogenic activity in lung cancer, and their expression is the net result of secretion by both malignant cells and infiltrating "normal" cells in the tumor stroma (Figure 1 *A*).

One of the more intriguing recent findings in this field is the discovery that specific chemokine ligand-receptor pairs dictate the organ-specific metastatic patterns of both breast and lung cancer.[14,15] In lung cancer, Phillips and colleagues showed that non-small cell lung cancer tumors and cell lines express the chemokine receptor CXCR4. Interestingly, CXCL12, the ligand for CXCR4, is constitutively expressed in the same tissues to which lung cancers preferentially metastasize (Figure 1 *B*). Antibody-mediated inhibition of CXCR4 in a mouse model of lung cancer dramatically reduced the incidence of tumor metastases.[15]

This topic covers only a small proportion of the extensive overlap between the disciplines of chemokine and tumor biology. Chemokines can also act as growth factors[16,17] and regulators of tumor immunity.[2] For a more in-depth review, see Balkwill.[18] The fundamental role(s) of chemokine ligand-receptor interactions in tumor biology suggests that targeting this biology is an important potential therapeutic opportunity for lung cancer. Therapeutic opportunities include approaches that target chemokines by blocking the proangiogenic chemokine receptor CXCR2 and/or the metastasis-promoting ligand receptor pair CXCL12/CXCR4. In addition, the interferon-inducible chemokines CXCL9, CXCL10, and CXCL11 should be explored as therapeutic agents themselves for their angiostatic and immunologic potential (immunoangiostasis of tumors). Each of these strategies has a sound rationale supported by current animal models and awaits further exploration at the level of human trials.

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